Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 61, 63-90 and 92-126 are pending in the application, with claims 61 and 90 being the independent claims. Claims 61 and 90 are sought to be amended by the present amendment. Claims 1-60, 62, and 91 were previously canceled without prejudice to or disclaimer of the subject matter therein.

Claims 61 and 90 have been amended to more clearly define Applicants' invention. Support for the amendments to claims 61 and 90 can be found in the specification, e.g., at page 4, lines 4-14; at page 5, line 12, to page 6, line 21; and at page 49, lines 1-5.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. The Claimed Invention

Applicants' invention as presently claimed is directed to high throughput, parallel screening methods for determining the pharmacological effects of test substances. The claimed methods are based on cellular assays and measure the effects of the test substances on the activities of biological target molecules in test cells. The claimed methods comprise (a) selecting from a cell population test cells of the same type by containing different biological target molecules (or of different types but containing the same biological target molecule); (b) applying test substances in parallel to one or more

sets of the test cells selected in (a), wherein a defined amount of a test substance from the same supply is applied simultaneously to a set of the test cells; (c) measuring the effects of the test substances applied in (b) on the biological activities of the biological target molecules (or on the activity of the biological target molecule) in the test cells using a detection system using different assays or assay formats; and (d) directly or indirectly comparing the effects of the test substances on the activities of the different biological target molecules (or on the activity of the biological target molecule) measured in (c).

In some embodiments (e.g., in the method of claim 61), the test cells contain different biological target molecules but are of the same type (see, e.g., the specification, at page 10, lines 9-17, and Example 1, at pages 25 to 43). In other embodiments (e.g., in the method of claim 90), the test cells contain the same biological target molecules but are of different types or of the same type but with a different state of differentiation or activation (see, e.g., the specification, at page 10, lines 19-31). A discussion of different biological target molecules appears in the specification, e.g., at page 9, lines 15-29; a discussion of cell types appears at page 8, lines 4-25.

A central feature of the claimed methods is that each test substance is applied *simultaneously* (*i.e.*, at the same time) to a set of test cells using the same source of test substance (see, e.g., the specification, at page 4, lines 10-13). In the method of claim 61, the set of test cells constitutes a group of test cells of the same type but containing different target molecules. In the method of claim 90, the set of test cells constitutes either (i) a group of test cells of different types which contain the same target molecule, or (ii) a group of test cells of the same type but with a different state of differentiation or activation, which contain the same biological target molecule.

Simultaneous application of each test substance to a set of different test cells (*i.e.*, application of the test substance to the different cells *at the same time*), using test substance from the *same source*, minimizes the variables associated with use of the different assays or assay formats that are required to measure the effect of the test substance in the different test cells. This allows for a better comparison and evaluation of the effect of the substance in the different test cells. See the specification, e.g., at page 4, lines 10-13, and page 6, lines 1-9.

Multiple test substances are then screened by parallel application to one or more sets of test cells ("parallel screening"), allowing for high throughput screening of the test substances. For example, the specification, at page 6, lines11-17, states that parallel screening is generally screening "whereby a number of different assays or assay formats are carried out with the same arrangement of equipment under the control of a robot." Thus, the claimed methods are typically carried out under the control of a robot.

II. Rejections under 35 U.S.C. § 102

Claims 61, 67-69, 74-76, 81-85, 87-89, 121, and 123-124 are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Weyer *et al.* (*Receptors and Channels*, Vol. 1, pp. 193-200 (1993)) ("Weyer"). (Office Action, at page 2, lines 21-22.) Applicants respectfully traverse this rejection.

Specifically, the Examiner states that "Weyer *et al.* teach high throughput parallel screening method (multiple well-format) of claims 61." (Office Action, at page 3, lines 1-2.) In particular, the Examiner alleges that Weyer teaches the limitations of step (b) of claim 61, stating:

> (b) applying from the same supply (from the same supply solution of phorobol ester PMA) a defined amount (10 ng/ml) of a test substance (phorobol ester PMA) in one operation (simultaneously) to more than one test cells of the same type comprising more than one cellular substrates (receptors), which differ in that they contain different target molecules (different receptors) (see page 199, col. 2, paragraph 1 under Luciferase assays, indicating treating isolated clones seeded in a 96 well format with a test compound);

(Office Action, at page 3, lines 10-15.) The Examiner goes on to allege that the specific limitations of the listed dependent claims are also taught, concluding that "Weyer *et al.* anticipates the instant claims." (Office Action, at page 3, line 1, to page 4, line 17.)

For rejections under 35 U.S.C. § 102, the Federal Circuit held "[a] claim is anticipated only if *each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 613, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added).

Applicants respectfully assert that Weyer fails to teach each and every element of the high throughput parallel screening method of pending claim 61, in particular, step (b), applying test substances in parallel to one or more sets of test cells containing different biological target molecules, wherein a defined amount of a test substance from the same supply is applied simultaneously to a set of said test cells containing different biological target molecules.

The passage in Weyer cited by the Examiner (*i.e.*, page 199, col. 2, paragraph 1 of Weyer, under the heading "Luciferase assays") states that cell clones were induced in triplicate "with the phorbol ester PMA (10 mg/ml) to detect clones expressing the luciferase gene alone *or with* neurokinin A (1 μM) *or* α-methylserotonin maleate (1 μM) to detect cell clones coexpressing the NK2 receptor *or* the 5-HT_2 receptor, *respectively*"

(emphasis added). The Examiner states in the Office Action, at page 13, that this passage "clearly [teaches] application of a test substance in one operation and assaying for the expression of different receptors in the cells treated with the test substance." (Office Action, at page 13, lines 13-15.)

Applicants respectfully disagree with the Examiner' interpretation of this passage. Applicants submit that this passage discloses application of one substance to cells expressing only one type of biological target molecule (here, a cloned receptor). First, the passage cited by the Examiner discloses that PMA was applied to cells expressing the luciferase gene alone, *i.e.*, PMA was applied to cells that were not expressing a biological target molecule. It does *not* disclose application of PMA to either of the two cell lines ("clones") expressing a biological target molecule, *i.e.*, to the cell line expressing the NK2 receptor or to the cell line expressing the 5-HT2 receptor. A close reading of the passage indicates that it was either neurokinin A (1 μM) *or* α-methylserotonin maleate (1 μM) - but *not* PMA - that was applied to the cell line expressing the NK2 receptor or to the cell line expressing the 5-HT_2 receptor. Second, the wording of the passage indicates that the neurokinin A was applied to cells of the clone expressing the NK2 receptor, and that the α-methylserotonin maleate was applied to cells of the clone expressing the 5-HT_2 receptor, respectively (*i.e.*, each substance was applied to cells containing the *same* biological target molecule). Neither neurokinin A nor α-methylserotonin maleate was applied to cells of *both* clones (*i.e.*, neither substance was applied to cells containing *different* biological target molecules, as recited in pending claim 61).

Thus, Applicants submit that, contrary to the Examiner's arguments, this passage of Weyer fails to teach each and every element of step (b) of the high throughput parallel screening method of pending claim 61: (b) applying test substances in parallel to one or more sets of test cells containing different biological target molecules, wherein a defined amount of a test substance from the same supply is applied simultaneously to a set of said test cells containing different biological target molecules.

The remaining text and figures in Weyer also fail to teach every element of Applicants' claimed parallel screening method. For example, the experiments disclosed on page 195, column 2, line 12, to page 196, column 2, line 4 of Weyer were conducted using recombinant cells engineered to express the NK2 receptor. Figure 1 shows the results of experiments in which various tachykinins (substance P, NKa and neuromedin K) were used to induce expression of luciferase in A20/NK2-122 cells expressing the NK2 receptor, while Figures 2a and 2b show the induction of luciferase expression in A20/NK2-122 cells in response to increasing doses of neurokinin receptor agonists (Fig. 2a) or antagonists after agonist-stimulation (Fig. 2b) of the cells. In each case, one or more test substances were applied to cells expressing the *same* biological target molecule (NK2 receptor) and *not* to a set of cells containing different biological target molecules as required by Applicants' claims. Similarly, the set of experiments disclosed on page 19, column 2, lines 5-28 (results presented in Figures 3a and 3b), were conducted using recombinant cells expressing the same biological target molecule, the 5-HT_2 receptor, rather than different biological target molecules.

Weyer, moreover, also fails to teach or suggest the application of a test substance to a set of test cells containing different biological target molecules *simultaneously* as required in (b) of claim 61.

In Weyer, there is no disclosure of applying a test agent *simultaneously* to a set of cells of the same type expressing different receptors. Instead, various comparisons are made from multiple experiments that appear to have been performed at different times. For example, in the Materials and Methods section on page 199 cited by the Examiner and discussed above, the luciferase assays are described as being performed with cells containing the NK2 receptors *or* the 5-HT_2 receptors, but there is no discussion of performing these tests by applying a test substance *simultaneously* to *both* cell lines.

At page 196, column 2, last line, to page 197, column 1, line 10, Weyer appears to describe experiments in which responses between two different receptor-containing cells were measured. This paragraph appears to disclose experiments in which test substances (PMA or forskolin) were applied to two cell lines expressing target molecules (A20/NK2-122 and A20/5HT2-11, expressing the NK2 receptor and 5-HT_2 receptor, respectively) and the responses of the cells were measured. There is no indication, however, that each test substance was applied *simultaneously* to *both* cell lines. To the contrary, Weyer states that "*several* sets of experiments" (emphasis added) were carried out to obtain the results (see page 196, column 2, last line). Applicants submit that if several sets of experiments were required to obtain the disclosed results, it is highly likely that each test substance was applied to both cell lines at different times rather than applied simultaneously.

Applicants thus submit that Weyer does not anticipate Applicants' pending claims because this reference fails to teach or suggest each and every element of the claims, in particular, the elements of applying a defined amount of a test substance from the same supply *simultaneously* to a set of the test cells containing *different* biological target molecules.

Applicants believe that the rejection of 61, 67-69, 74-76, 81-85, 87-89, 121, and 123-124 under 35 U.S.C. § 102(b) has been overcome and respectfully request that the rejection be withdrawn.

III. Rejections under 35 U.S.C. § 103

In re Vaeck (947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)) outlines the factors required for establishing a *prima facie* case for obviousness: prior art references that teach all claim limitations, a motivation to combine the teachings in the references themselves or knowledge known to a person of skill in the art at the time the invention was made, and a reasonable expectation of success from the combination of elements in the references. As discussed below, Applicants respectfully assert that these requirements have not been met to support a *prima facie* argument for obviousness for the instant claims.

A. Weyer in view of Johnson

Claims 63, 64, 66, 70, 77-80, 90, 92, 93, 95-99, 103-114, 116-120, 122, 125, and 126 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Weyer in view of Johnson, International Publ. No. WO 95/28421 ("Johnson"). (Office Action, at page 5, lines 10-12.) Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that Johnson teaches a method of determining the pharmacological effect of a substance on the activity of different biological target molecules in the signal transduction pathway wherein said different target molecules comprise a receptor-coupled signal transduction pathway. (Office Action, at page 7, lines 11-15.) The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Weyer with a step of including cells comprising various signaling molecules that control cell differentiation/growth/apoptosis as taught by Johnson. (Office Action, at page 8, lines 1-4.)

The deficiencies of Weyer have been discussed *supra* and remain applicable in the present rejection. Johnson fails to teach or suggest simultaneous application of a test substance from the same supply to a set of different test cells, as required by Applicants' claims. Johnson merely characterizes the response of various second messenger protein kinases to various stimuli and putative regulatory compounds. *See* Johnson, at page 61, line 16 to page 62, line 23. Thus, Applicants submit that Johnson fails to overcome the deficiencies of Weyer. Because no combination of these references would arrive at the claimed invention, the burden of a *prima facie* case for obviousness has not been met.

Accordingly, Applicants believe that the rejection of claims 63, 64, 66, 70, 77-80, 90, 92, 93, 95-99, 103-114, 116-120, 122, 125, and 126 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Weyer in view of Johnson has been overcome and respectfully request that the rejection be withdrawn.

B. Weyer in view of Johnson and in further view of Bischoff and Brown

Claims 65, 71-73, 94, and 100-102 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weyer in view of Johnson and in further view of Bischoff *et al.*, U.S. Pat. No. 5,705,342 ("Bischoff"), and Brown *et al.*, U.S. Pat. No. 5,929,081 ("Brown"). (Office Action, at page 8, lines 15-19.) Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that Bischoff teaches regulation of cell proliferation control and neoplasia by Bcl-2 expression and signal transduction mediated by the association between Ras and bcl-2 (Office Action, at page 9, lines 3-5), while Brown teaches a method for treating diseases mediated by cellular proliferation signal transduction pathway effector molecules, comprising treating the diseases associated with cellular target receptor molecules such as VGEF, HER2, and ras/raf pathway signalling molecules (Office Action, at page 9, lines 6-9).

The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Weyer in view of Johnson with a step of including Bcl-2 as taught by Bischoff and receptors as HGF, HER2 and KDR as taught by Brown to enhance the sensitivity of the method to detect the signaling pathway as a whole. (Office Action, at page 9, lines 11-14.)

The deficiencies of Weyer and Johnson have been discussed *supra* and remain applicable in the present rejection. Applicants submit that Bischoff and Brown do not remedy the deficiencies of Weyer and Johnson because neither Bischoff nor Brown teaches application of a test substance from the same supply, applied simultaneously to a set of different test cells, as required by Applicants' claims. Thus, Applicants submit that

Johnson fails to overcome the deficiencies of Weyer. Because no combination of these four references would arrive at the claimed invention, the burden of a *prima facie* case for obviousness has not been met.

Accordingly, Applicants believe that the rejection of claims 65, 71-73, 94, and 100-102 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weyer in view of Johnson and in further view of Bischoff and Brown has been overcome and respectfully request that the rejection be withdrawn.

C. Weyer in view of Chalfie

Claim 86 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weyer in view of Chalfie *et al.*, U.S. Pat. No. 5,491,084 ("Chalfie"). (Office Action, at page 10, lines 6-7.) Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that Chalfie teaches a method for cells expressing a biological activity (gene expression) of a particular target molecule, wherein the regulatory sequences of a target molecule are linked to a reporter fluorescent protein which fluoresces when the target is expressed within the cells, and that the reporter fluorescent protein is a gene encoding a green fluorescent protein. (Office Action, at page 10, lines 11-14.)

The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of determining the effect of a substance on the biological activities of target molecules as taught by Weyer with the method of detecting the effect of a substance on different target molecules linked to a GFP reporter gene system as taught by Chalfie to achieve an enhanced

sensitivity in determining the effect of a substance on biological activity. (Office Action, at page 10, lines 16-21.)

The deficiencies of Weyer have been discussed *supra*. Chalfie merely teaches the use of green fluorescent protein ("GFP") as a reporter gene. Chalfie fails to teach application of a test substance from the same supply, applied simultaneously to a set of different test cells, as required by Applicants' claims. Applicants submit, therefore, that Chalfie cannot be used to remedy the specific deficiencies of Weyer. Since the combination of Weyer and Chalfie does not teach each and every element of the claims, Applicants thus assert that the Examiner has not met the burden for a *prima facie* case for obviousness.

Accordingly, Applicants believe that the rejection of claim 86 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weyer in view of Chalfie has been overcome and respectfully request that the rejection be withdrawn.

D. Weyer in view of Johnson in further view of Chalfie

Claim 115 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weyer in view of Johnson and in further view of Chalfie. Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of determining the effect of a substance on the biological activities of target molecules as taught by Weyer in view of Johnson with the method of detecting the effect of a substance on different target molecules linked to a GFP reporter gene system as taught

by Chalfie to achieve an enhanced sensitivity in determining the effect of a substance on biological activity. (Office Action, at 1-6.)

The deficiencies of Weyer in view of Johnson have been discussed *supra*. Also, as discussed *supra*, Chalfie merely teaches the use of GFP as a reporter gene. Chalfie fails to teach application of a test substance from the same supply, applied simultaneously to a set of different test cells, as required by Applicants' claims. Applicants therefore submit that Chalfie fails to remedy the specific deficiencies of Weyer, even in view of Johnson. Therefore, since this combination of references does not teach each and every element of the claims, Applicants assert that the Examiner has not met the burden for a *prima facie* case for obviousness.

Accordingly, Applicants believe that the rejection of claim 115 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weyer in view of Johnson and in further view of Chalfie has been overcome and respectfully request that the rejection be withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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